92. A method for the treatment of human mammary carcinoma comprising administering to a human in need thereof a DNA construct comprising a therapeutic gene placed under transcriptional control of a rodent MMTV regulatory sequence, wherein the therapeutic gene is expressed in human mammary carcinoma cells and the human mammary carcinoma is treated.

93. A method for expression of a heterologous gene in a human mammary cell comprising introducing a vector comprising the gene under transcriptional control of a rodent WAP regulatory sequence into the cell and maintaining the cell under conditions in which the heterologous gene is expressed in the human mammary cell.

94. A method for the treatment of human mammary carcinoma comprising administering ~~to a~~ human in need thereof a DNA construct comprising a therapeutic ~~gene~~ placed under transcriptional control of a rodent WAP ~~regulatory~~ sequence, wherein the therapeutic gene is expressed in human ~~mammary~~ carcinoma cells and the human mammary carcinoma is ~~treated.~~---

REMARKS

Information Disclosure Statement

Applicants direct the Examiner's attention to the Information Disclosure Statement (IDS) being filed concurrently herewith which includes a Transmittal Letter and PTO form 1449. Applicants further direct the Examiner's attention to page 2 of the Transmittal Letter wherein pending applications are cited.

Applicants respectfully request that, in addition to initialing the references listed on PTO form 1449, the Examiner also initial the references on page 2 of the Transmittal Letter to indicate that the Examiner considered the pending applications and include a copy of the initialed page 2 of the Transmittal letter along with the copy of the initialed PTO form 1449 with the next Office Action.

Objection of Claim 31

Claim 31 is objected to as depending on Claim 36 "which is not a preceding claim" (Office Action, page 2).

Claim 31 has been amended to depend from Claim 27, thereby obviating the objection.

Rejection of Claims 2, 10, 11, 18, 19, 31, 32, 44, 45, 55 and 56 under 35 U.S.C. §112, second paragraph

Claims 2, 10, 11, 18, 19, 31, 32, 44, 45, 55 and 56 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 3).

The Examiner states that Claim 18 is indefinite because it "depends on a canceled claim 20", and Claim 19 is indefinite because it depends from Claim 18 (Office Action, page 3).

Claim 18 has been amended to depend from Claim 16 thereby obviating the rejection.

The Examiner states that the phrase "The according" in Claim 27 renders the claim indefinite.

Claim 27 has been amended to recite the phrase "The method according...", thereby obviating the rejection.

The Examiner states that the phrase "proximal 445 bp of the WAP promoter" in Claims 2, 44 and 55 is vague and renders the claims indefinite because it "is unclear what 445 bp of which WAP promoter is intended" (Office Action, page 3). In the previously filed Amendment A mailed to the Patent Office on December 8, 1999, Applicants deleted the phrase from Claim 2. Claims 44 and 55 have been amended to indicate that the WAP promoter is of murine origin.

The Examiner states that the phrase "320 bp XhoI/XbaI fragment of the WAP promoter" in Claims 45 and 56 "is vague and renders the clams indefinite" because it "is unclear what 320 bp XhoI/XbaI fragment of which WAP promoter is intended" (Office Action, page 3).

Claims 45 and 56 have been amended to indicate that the WAP promoter is of murine origin.

The Examiner states that there is insufficient basis for the phrase "therapeutic gene" in Claims 31 and 32.

Claim 31 has been amended to depend from Claim 27, thereby obviating the rejection.

Rejection of Claims 41-52 under 35 U.S.C. §112, second paragraph

Claims 41-52 are rejected under 35 U.S.C. §112, second paragraph "as being incomplete for omitting essential steps, such omission amounting to a gap between the steps" (Office Action, page 3). The Examiner states that the claims "fail to teach any steps for delivery of the

expression construct containing the heterologous gene and WAP regulatory sequence to a human mammary cell, whereby after the delivery of the expression provides for gene expressing in the human mammary cell" (Office Action, page 4).

Claim 41 has been amended to recite a method for expression of a heterologous gene in a human mammary cell comprising introducing a vector comprising the gene under transcriptional control of a WAP regulatory sequence into the cell and maintaining the cell under conditions in which the heterologous gene is expressed in the human mammary cell.

Rejection of Claims 23-25, 37-40 and 67-73 under 35 U.S.C. §112, first paragraph

Claims 23-25, 37-40 and 67-73 are rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention" (Office Action, page 4). The Examiner states that Applicants' position that the data in the specification reasonably correlates to expressing a heterologous gene in a human cell and/or treating human mammary carcinoma is not persuasive "because the specification of the present application only discloses the construction of vectors pMMTV-BAG and pWAP-BAG containing β-galactosidase gene under the control of a MMTV and a WAP promoter, respectively" (Office Action, page 5). The Examiner further states that the "specification fails to provide adequate guidance and fails to demonstrate data for the treatment of disorders or diseases of human mammary cells with a DNA construct comprising a therapeutic gene under the control of a MMTV promoter or a WAP promoter, a viral particle containing said DNA construct, cells containing said DNA construct and encapsulated cells, and show the therapeutic effect of said treatment *in vitro* or *in vivo*" (Office Action, page 5). It is the Examiner's opinion that the "expression of a β-galactosidase in explanted normal primary human mammary tissue infected with vectors pMMTV-BAG and pWAP-BAG is not considered to enable therapeutic gene expression under the control of a MMTV promoter or a WAP promoter, since expression of a marker gene does not correlate with expression of a gene *in vivo*, such that the expression provides for a therapy" (Office Action, page 6). The Examiner concludes that:

> [i]n view of the lack of guidance in the specification on how to treat the disorders or diseases of human mammary cells with encapsulated cells containing a construct comprising a therapeutic gene under control of a MMTV promoter or a WAP promoter and the human unpredictability in art, it would have required undue experimentation for one skilled in the art at the time of the invention to have made a DNA construct or a recombinant viral vector comprising at least one

> therapeutic gene under transcriptional control of a MMTV or a WAP regulatory sequence, a retroviral particle or cells containing said DNA construct or viral vector, encapsulated cells comprising a core containing said cells to treat disorders or diseases of human mammary cells including human mammary carcinoma, and exhibited therapeutic effect of said treatment *in vivo*. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art (Office Action, page 9).

Applicants respectfully disagree. It is known in the art that the β-galactosidase (β-gal) gene can be of therapeutic relevance after viral vector delivery (see Chen *et al., J. Immunol., 156:*224-231 (1996), which is being filed herewith as Exhibit A). Furthermore, as discussed in the previously filed Amendment A, in the specification as filed Applicants describe how they made a retroviral construct in which the β-gal gene is placed under transcriptional control of a WAP or a MMTV regulatory sequence (see Examples 1-3); how they made retroviral particles produced by culturing a packaging cell line harboring the retroviral vector and one or more constructs coding for proteins required for the retroviral vector to be packaged; and how virus containing supernatant was used to infect mammary tissue. Applicants demonstrated that "the WAP regulatory elements as well as the MMTV-U3 region can drive expression of a gene within a MLV retroviral vector in primary human mammary gland cells" (specification, page 31, lines 6-9). Applicants further describe how to make a retroviral vector carrying the rat cytochrome P450 gene under control of the WAP regulatory sequence; and how to encapsulate a cell line containing the claimed construct and implant the capsules producing viral particles in or around mammary tissue to ensure continuous release of virus (Example 5).

Using Applicants' disclosure as a guide, a person of skill in the art can prepare Applicants' claimed pharmaceutical composition and use the compositions in the claimed methods of treatment without undue experimentation. In addition, a person of skill in the art would reasonably conclude from Applicants' data that the claimed construct can be used for the treatment of human mammary carcinoma.

The Examiner further states that "the state of the art of gene therapy at the time of the invention was unpredictable" (Office Action, page 6). The Examiner cites Orkin *et al.* as reporting that "none of the available vector systems for gene transfer is *entirely satisfactory*, and many of the perceived advantages of vector systems have not been experimentally validated"

(Office Action, page 6, emphasis added). In the paragraph bridging pages 6-7 of the Office Action, the Examiner refers to various problems associated with gene transfer efficiency.

However, there is no nexus between the general problem scenarios envisioned by the Examiner and Applicants' claimed invention. Furthermore, it is not a requirement of U.S. patent law that Applicants' claimed constructs be *entirely satisfactory* for use in the claimed methods of treatment. The court has clearly stated that:

> There is nothing in the patent statute . . . which gives the Patent Office the right or the duty to require an applicant to prove what compounds or other materials which he is claiming, and which he has stated are useful "pharmaceutical applications," are safe, effective, and reliable for use with humans. It is not for us or the Patent Office to legislate and if the Congress desires to give this responsibility to the Patent Office, it should do so by statute (*In re Krimmel*, 130 U.S.P.Q. 215 at 220 (CCPA 1961)).

Orkin *et al.* provide a general discussion of gene therapy in order to assess the NIH investment in research on gene therapy. Orkin *et al.* do not discuss Applicants' claimed invention, and thus, is not relevant to Applicants' claimed invention. Nevertheless, Applicants direct the Examiner's attention to Table 1 of the Orkin *et al.* reference which lists the advantages and disadvantages of several vector systems in use or under consideration for gene therapy. This teaching in the Orkin *et al.* reference is sufficient to establish that one of skill in the art would reasonably expect that foreign genes could delivered and expressed in target cells using known vectors. Applicants further direct the Examiner's attention to Exhibit A, wherein Chen *et al.* teach that:

> recombinant adenovirus has been used as a vector for delivery of gene therapy in patients with cystic fibrosis, atherosclerosis disease, and α_1-antitrypsin deficiency, among others. With genetic deletions that attenuate the virus and subsequent insertions of new genetic material, rAd effectively expresses these heterologous proteins in vitro and in vivo with relatively few apparent side effects (Chen *et al.*, page 224, column 2).

Regarding the encapsulation of Applicants' claimed compositions, the Examiner states that Aebischer *et al.* report "various problems of encapsulated cells for the treatment of disorder or diseases" (Office Action, page 7). The Examiner notes that Shao *et al.* teach that encapsulated cells may be used for prolonged delivery of GM-CSF to a tumor site, but chooses to give more weight to the teachings of the Aebischer *et al.* reference. Determination of enablement is based on evidence as a whole.

Nevertheless, like Shao *et al.*, Aebischer *et al.* is a proponent of the encapsulation process for methods of treatment. For example, Aebischer *et al.* teach that "[c]omparison of micro- versus macrocapsules with PC12 cells shows that both types of capsule allow the

transplanted cells to survive and improve the behavior of experimentally-induced parkinsonism in rats"; that "macroencapsulated PC12 cells improve the parkinsonian symptomatology of MPTP lesioned, non-human primates"; that "the encapsulation technique is not limited to neurotransmitter cells"; and that "[n]eurotrophic factors, which may prevent the progression of neurodegenerative diseases . . . could be delivered to specific brain targets through the transplantation of cells engineered to secrete the appropriate factor" (Aebischer *et al.*, page 182, column 1).

Clearly, the art shows that those of skill in the art would reasonably predict from Applicants' data that Applicants' claimed pharmaceutical compositions and methods of treatment would exhibit a therapeutic effect on treating diseases of human mammary cells. In addition, Applicants have provided sufficient guidance for carrying out the claimed invention.

It is the Examiner's opinion that "[t]he quantity of experimentation required to practice the invention as claimed would include isolation of any therapeutic gene which is yet to be identified, [and] determination of the function of said therapeutic gene" (Office Action, page 8). However, those of skill in the art know of many therapeutic genes which can be used in Applicants' claimed invention, and Applicants have provided specific examples of such therapeutic genes in the specification as filed (specification, page 7, line 22 -page 8, line 2). In addition, the court has clearly stated that the Patent Office cannot use later art-related facts that did not exist as of the filing date to test an application for compliance with the requirements of 35 U.S.C. §112 (*In re Hogan*, 194 U.S.P.Q. 527 at 538 (CCPA 1977)).

The Examiner further states that the quantity of experimentation required to practice the invention as claimed would also include generation of a DNA construct or a recombinant viral vector comprising at least one therapeutic gene under transcriptional control of a MMTV or a WAP regulatory sequence, generation of a retroviral particle or cells containing said DNA construct or viral vector, generation of encapsulated cells comprising a core containing said cells, determination of therapeutic effects said DNA construct, viral vector and encapsulated cells on treating disorders or diseases of human mammary cells including human mammary carcinoma *in vivo*" (Office Action, pages 8-9).

As discussed above, in the specification as filed Applicants describe how they made a retroviral construct in which the β-gal gene is placed under transcriptional control of a WAP or a MMTV regulatory sequence (see Examples 1-3); and how they made retroviral particles produced by culturing a packaging cell line harboring the retroviral vector and one or more

constructs coding for proteins required for the retroviral vector to be packaged, wherein virus containing supernatant was used to drive expression of a gene in primary human mammary gland cells. Applicants further describe how to make a retroviral vector carrying the rat cytochrome P450 gene under control of the WAP regulatory sequence; and how to encapsulate a cell line containing the claimed construct and implant the capsules producing viral particles in or around mammary tissue to ensure continuous release of virus (Example 5).

Based on the guidance provided in Applicants' disclosure, a person of skill in the art is enabled to practice Applicants' claimed invention without undue experimentation.

As indicated in the previously filed Amendment A, when an enablement rejection is made based on a reason to doubt the objective truth of statements contained in Applicants' specification, "it is incumbent upon the Patent Office . . .to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement" (*In re Marzocchi & Horton* 169 USPQ 367, 369 (CCPA 1971)). The Examiner has failed to meet the initial burden of providing acceptable evidence or reasoning as to why the truth or accuracy of any statement in a supporting disclosure is doubted. Indeed, the art of record indicates that one of skill in the art would reasonably conclude from Applicants' data that the claimed constructs and pharmaceutical compositions can be used for the treatment of human mammary carcinoma.

Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Rejection of Claims 26-33, 36 and 41-52 under 35 U.S.C. §112, first paragraph

Claims 26-33, 36 and 41-52 are rejected under 35 U.S.C. §112, first paragraph "because the specification, while being enabling for the expression of a β-galactosidase in normal primary human mammary gland cells infected with the vectors pWAP-BAG and pMMTV-BAG *in vitro*, does not reasonably provide enablement for expression of any gene in any human cell under the control of any WAP promoter derived from any organism other than mouse or a MMTV promoter" (Office Action, pages 9-10). The Examiner states that:

> [t]he specification fails to provide adequate guidance and demonstration as to whether any WAP promoter derived from any organism other than mouse can direct gene expression in any human cell type other than normal human mammary gland cells. The specification also fails to teach a utility for the *in vivo* expression of β-galactosidase gene under control of either a MMTV or WAP promoter (Office Action, pages 10-11).

The Examiner further states that:

> gene expression via a MMTV promoter in normal human mammary gland cells do not necessarily imply that the MMTV promoter can direct gene expression in other human cell types or in malignant tumor cells. Further, the MMTV promoter is known in the art to be a mammary cell-specific promoter, it is likely that the MMTV promoter can not direct gene expression in any human cell type other than mammary cells (Office Action, page 11).

Applicants respectfully disagree. Applicants direct the Examiner's attention to Mrochen *et al., J. Mol. Med., 75:*820-828 (1997), which is co-authored by two of the inventors of the subject application and is being filed concurrently herewith as Exhibit B, wherein it is demonstrated that the MMTV regulatory sequence was used to infect human bladder carcinoma cells. In the specification as filed, Applicants describe how they made a retroviral construct in which the β-gal gene is placed under transcriptional control of a WAP or a MMTV regulatory sequence (see Examples 1-3); and how they made retroviral particles produced by culturing a packaging cell line harboring the retroviral vector and one or more constructs coding for proteins required for the retroviral vector to be packaged, wherein virus containing supernatant was used to drive expression of a gene in primary human mammary gland cells (Example 4). Applicants further describe how to make a retroviral vector carrying the rat cytochrome P450 gene under control of the WAP regulatory sequence; and how to encapsulate a cell line containing the claimed construct and implant the capsules producing viral particles in or around mammary tissue to ensure continuous release of virus (Example 5). In addition, it is known in the art that the β-galactosidase (β-gal) gene can be of therapeutic relevance after viral vector delivery (see Chen *et al.* being filed herewith as Exhibit A).

Using the guidance provided in the specification as filed and routine methods, a person of skill in the art can make a construct in which a known heterologous gene is under transcriptional control of a WAP or a MMTV promoter derived from any organism other than mouse and assess whether the WAP or MMTV promoter directs gene expression in any human cell type other than normal human mammary gland cells. The Examiner has not provided acceptable evidence or reasoning as to why the truth or accuracy of Applicants' claimed invention is doubted.

The Examiner refers to Applicants' teaching in the specification that it is unpredictable that the WAP promoter would function at all to direct expression in human mammary cells and/or allow expression in human mammary carcinoma cells (specification, page 2, lines 22-25). However, this was prior to Applicants' discovery that "the WAP regulatory sequence is able to direct expression of a linked heterologous gene in primary human cells, including mammary

carcinoma cells" (specification, page 2, line26 - page 3, line 2), upon which the claimed invention is based.

Furthermore, as amended the claims relate to a method for the expression of a heterologous gene in a human cell comprising introducing a retroviral vector comprising said gene under transcriptional control of an MMTV regulatory sequence into the human cell and maintaining the cell under conditions in which the heterologous gene is expressed in the human cell; and a method for expression of a heterologous gene in a human mammary cell and a method for expression of a heterologous gene in a human mammary cell comprising introducing a vector comprising the gene under transcriptional control of a WAP regulatory sequence into the cell and maintaining the cell under conditions in which the heterologous gene is expressed in the human mammary cell. If a particular gene under transcriptional control of a particular WAP or MMTV regulatory sequence is not expressed in a human cell or a human mammary cell, then the construct does not fall within the scope of Applicants' claimed invention, particularly as amended.

The Examiner further states that:

> [t]he quantity of experimentation required for the invention as claimed includes isolation of putative WAP promoters and downstream genes, identification of WAP promoters derived from various organisms, sequencing of the potential DNA sequences, determination of the WAP promoter function in its native cells, construction of an expression vector containing any heterologous gene under the control of a MMTV promoter and determination of the expression of said gene in various types of normal human cells and tumor cells (Office Action, page 12).

Applicants respectfully disagree. At the time of Applicants' invention, WAP genes other than the murine WAP gene were known to those of skill in the art (see Simpson *et al., J. Mol. Endocrinol., 20:*27-35 (1998), which is being filed herewith as Exhibit C). To recite a murine WAP regulatory sequence would unduly limit Applicants' claimed invention and invite one of skill to easily design around the invention. For example, a person of skill could use the WAP regulatory sequence of camel, rabbit or pig to easily get around such a claimed invention. Based on Applicants' data a person of skill in the art would reasonably expect that a WAP regulatory sequence other than the murine WAP regulatory sequence will direct expression of a known therapeutic gene in a human cell. Furthermore, as discussed above, Applicants have provided sufficient guidance in the specification as filed to a person of skill in the art for preparing the claimed compositions and carrying out the claimed methods. Using Applicants' disclosure, a

person of skill in the art can prepare a construct using a WAP regulatory sequence other than the murine WAP regulatory sequence and use the construct in Applicants' claimed methods.

Applicants have provided an enabling disclosure for the full scope of the claimed invention

Rejection of Claims 1, 2, 4, 5, 9-14 and 16-19 under 35 U.S.C. §103(a)

Claims 1, 2, 4, 5, 9-14 and 16-19 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Dranoff et al., 1993 (U2) in view of Lefebvre et al., 1991 (V2) and Shao et al., 1994 (X2)" (Office Action, page 13). The Examiner states that Dranoff *et al.* teach subcloning DNA sequences encoding cytokines and adhesion molecules into the retroviral vector MFG which contains the Mo-MuLV LTR and introducing the resulting construct into CRIP packaging cells to generate recombinant virus which are used to transfect B16 melanoma cells. The Examiner notes that the transduced B16 cells are inoculated into C57BL/6 mice to monitor the delay of tumor formation associated with the synthesis of cytokine transgene, but do not teach using MMTV or WAP promoter for the expression of a gene product in mammary gland. The Examiner cites Lefebvre *et al.* as revealing the presence of MMTV promoter and the positive and negative regulatory regions upstream of the MMTV promoter. The Examiner cites Shao *et al.* as teaching microcapsules composed of collagen and encapsulated B16-F10 cells transduced with retrovirus containing GM-CSF gene into said microcapsule, and the monitoring of GM-CSF secretion in the culture medium. It is the Examiner's opinion that:

> [i]t would have been obvious to a person ordinary skill in the art at the time the invention was made to substitute the Mo-MuLV LTR with the MMTV promoter and use with any desired gene for the construction of a recombinant retroviral vector, a recombinant retrovirus containing said retroviral vector or packaging cells harboring said retroviral vector, and a capsule encapsulating said packaging cells for the expression of any desired gene product in mammary cells *in vitro* or *in vivo*, because Mo-MuLV LTR and MMTV promoter both are regulatory sequences derived from LTR and they both have function of directing gene expression. Generation of an isolated human cell comprising a retroviral provirus containing a heterologous gene under control of a MMTV promoter would have been obvious for a person of ordinary skill at the time of the invention because the claim does not specify that the gene has to be expressed, one could generate an isolated human cell comprising said retroviral provirus just to determine if said gene can be expressed in a human cell (Office Action, pages 14-15).

The Examiner further states that one having ordinary skill would have been motivated to do this in order to produce the retroviral vector, retroviral particle, retroviral provirus and packaging cell line as taught by Dranoff *et al.* and a capsule as taught by Shao *et al.* for generating a potent,

specific and long lasting anti-mammary tumor immunity as taught by Dranoff *et al.* and Lefebvre *et al.* (Office Action, page 15).

Applicants respectfully disagree. As amended, the claims relate to a retroviral vector comprising a heterologous gene placed under transcriptional control of an MMTV regulatory sequence, wherein the MMTV regulatory sequence directs expression of the heterologous gene in a cell when the vector is introduced into the cell.

As pointed out in the previously filed Amendment A, that the *rodent* MMTV regulatory sequence can direct expression of a heterologous gene in *human* cells or that the MMTV regulatory sequence would do so using a retroviral vector, is not made obvious by the cited prior art. *It appears, however, that the Examiner has repeated the obviousness rejection, but has not addressed Applicants' rebuttal of the obviousness rejection.* Specifically, Applicants request that the Examiner direct Applicants' attention to the motivation to substitute the Mo-MuLV LTR with the MMTV promoter and use with any desired gene for the construction of a recombinant retroviral vector *which is present in the cited art.* The Examiner states that the substitution would be obvious "because Mo-MuLV LTR and MMTV promoter both are regulatory sequences derived from LTR and they both have function of directing gene expression" (Office Action, page 15). Applicants respectfully submit that this reasoning does not support the Examiner's obviousness rejection. The issue of an obviousness rejection is "whether the teachings of the prior art would, *in and of themselves and without the benefit of appellant's disclosure,* make the invention as a whole, obvious" (*In re Sponnoble* 160 USPQ237 at 243 (CCPA 1969)).

Dranoff *et al.* show that in B16 melanoma cells, in which nontransduced irradiated cells possess little ability to stimulate systemic anti-tumor immunity, a previously unidentified molecule, murine granulocyte-macrophage CSF (GM-CSF), is the most potent stimulator of systemic anti-tumor immunity of the 10 molecules tested (Dranoff *et al.*, page 3539, column 2). Dranoff *et al.* used the Mo-MuLV LTR to express the 10 molecules in the model (Dranoff *et al.*, Figure 1), and as noted by the Examiner, do not teach "using MMTV promoter for the expression of a gene in a retroviral vector, and a capsule encapsulating the packaging cell line, said capsule comprising a porous capsule wall surrounding said packaging cell line" (Office Action, page 14).

Using a series of mammary and nonmammary murine cell lines, Lefebvre *et al.* identified two elements, located upstream of the hormone responsive element, that specifically regulate the MMTV promoter. Lefebvre *et al.* do not teach or even suggest that the MMTV promoter can be used to express a heterologous gene in a human cell.

Shao *et al.* studied whether prolonged delivery of GM-CSF can be achieved by encapsulating GM-CSF-secreting cells in semi-permeable macrocapsules (Shao *et al.*, page 59, column 1). Based on their results, Shao *et al.* teach that their study "demonstrates the merit of this cell encapsulation system" and "suggests an alternative mode of cytokine delivery and provides basis for other cell-based artificial organ designs" (Shao *et al.*, page 60, column 1). Shao *et al.* do not discuss use of the MMTV regulatory sequences for any purpose.

Where the claimed invention is rejected as obvious in view of a combination of references, § 103 requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success (*In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.*

There are no teachings in the art cited which, in and of themselves, would direct the skilled person to obtain expression of a heterologous gene in human cells using the rodent MMTV regulatory sequence or use a retroviral vector to do so. MMTV is a rodent regulatory sequence and the cited art provides no suggestion or expectation of success that the rodent regulatory sequence can direct expression of a heterologous gene in human cells.

Dranoff *et al.* and Shao *et al.* do not even mention the MMTV promoter or the use thereof for any purpose. Thus, the teachings in the Dranoff *et al.* and Shao *et al.* references are not relevant to Applicants' invention. Lefebvre *et al.* identified two region of the MMTV LTR that regulate its promoter activity in murine cells, but do not teach or even suggest that the MMTV promoter can be used to express a heterologous gene in a human cell. Clearly, the combined teachings of the cited references, either alone or in combination, do not teach or even suggest expression of a heterologous gene in human cells using the rodent MMTV regulatory sequence.

As stated in the previously filed Amendment A, the obviousness rejection has been made with the advantage of impermissible hindsight, and is therefore, legally improper. That is, in making the obviousness rejection, the Examiner has read the prior art with the benefit of Applicants' disclosure in which there is a clear teaching that the rodent MMTV regulatory sequences can direct expression of a heterologous gene in human cells and that the MMTV regulatory sequences would do so using a retroviral vector. As the court made clear in *In re Dow*, it is not legally correct to rely on Applicant's disclosure for the suggestion that the cited references should be combined and the expectation of success. In the present case, the

suggestion or motivation for combining the references and the expectation of success are not found in the prior art, but rather in Applicant's disclosure.

The combined teachings of Dranoff *et al.* in view of Lefebvre *et al.*, 1991, Shao *et al.* 1994 do not render obvious Applicants' claimed invention.

Rejection of Claims 53-66 under 35 U.S.C. §103

Claims 53-66 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Dranoff et al. 1993 (U2) in view of Paleyanda et al., 1994 (W2) and Shao et al., 1994 (X2)" (Office Action, page 15). The Examiner states that Dranoff *et al.* teach subcloning DNA sequences encoding cytokines and adhesion molecules into the retroviral vector MFG which contains the Mo-MuLV LTR and introducing the resulting construct into CRIP packaging cells to generate recombinant virus which are used to transfect B16 melanoma cells. The Examiner notes that the transduced B16 cells are inoculated into C57BL/6 mice to monitor the delay of tumor formation associated with the synthesis of cytokine transgene, but do not teach using MMTV or WAP promoter for the expression of a gene product in mammary gland. The Examiner cites Paleyanda *et al.* as teaching construction of a plasmid containing the HPC gene under the control of mouse WAP promoter for making a transgenic mouse expressing HPC and that HPC mRNA is detected mainly in the mammary gland. The Examiner cites Shao *et al.* as teaching microcapsules composed of collagen as the internal layer and a synthetic polyelectrolyte as the external layer that cen be optimized for stability and transport properties, the encapsulation of B16-F10 cells transduced with retrovirus containing GM-CSF gene into said microcapsule, and the monitoring of GM-CSF secretion in the culture medium. It is the Examiner's opinion that:

> [i]t would have been obvious to a person ordinary skill in the art at the time the invention was made to substitute the Mo-MuLV LTR with the WAP promoter to combine with any desired gene for the construction of a recombinant retroviral vector, a recombinant retrovirus containing said retroviral vector, or packaging cells harboring said retroviral vector, and a capsule encapsulating said packaging cells for the expression of any desired gene product in mammary cells *in vitro* or *in vivo*, because Mo-MuLV LTR and WAP promoter both are regulatory sequences derived from LTR and they are similar structurally. Using various region of the WAP LTR would have been obvious for a person of ordinary skill because one would use various WAP promoter regions for the expression of a desired gene product in order to optimize the enhancer or promoter activity of WAP promoter. Furthermore, generation of an isolated human cell comprising a retroviral provirus containing a heterologous gene under control of a WAP promoter would have been obvious for a person of ordinary skill at the time of the invention because the claims does not specify that the gene has to be expressed,

> one could generate an isolated human cell comprising said retroviral provirus just to determine if said gene can be expressed in a human cell (Office Action, pages 14-15).

The Examiner further states that one having ordinary skill would have been motivated to do this in order to produce the retroviral vector, retroviral particle, retroviral provirus and packaging cell line as taught by Dranoff *et al.* and a capsule as taught by Shao *et al.* for the study of a method which generates a potent, specific and long lasting anti-mammary tumor immunity as taught by Dranoff *et al.* and Paleyanda *et al.* (Office Action, page 18).

Applicants respectfully disagree. As amended, the claims relate to a retroviral vector comprising a heterologous gene placed under transcriptional control of a WAP regulatory sequence, wherein the WAP regulatory sequence directs expression of the heterologous gene in a cell when the vector is introduced into the cell.

As pointed out in the previously filed Amendment A, that the *rodent* WAP regulatory sequence can direct expression of a heterologous gene in *human* cells or that the WAP regulatory sequence would do so using a retroviral vector, is not made obvious by the cited prior art. *It appears, however, that the Examiner has repeated the obviousness rejection, but has not addressed Applicants' rebuttal of the obviousness rejection.* Specifically, Applicants request that the Examiner direct Applicants' attention to the motivation to substitute the Mo-MuLV LTR with the WAP promoter and use with any desired gene for the construction of a recombinant retroviral vector *which is present in the cited art*. The Examiner states that the substitution would be obvious "because Mo-MuLV LTR and WAP promoter both are regulatory sequences derived from LTR and they both have function of directing gene expression" (Office Action, page 15). Applicants respectfully submit that this reasoning does not support the Examiner's obviousness rejection. The issue of an obviousness rejection is "whether the teachings of the prior art would, *in and of themselves and without the benefit of appellant's disclosure,* make the invention as a whole, obvious" (*In re Sponnoble* 160 USPQ237 at 243 (CCPA 1969)).

Applicants respectfully disagree. The combined teachings of Dranoff *et al.* and Shao *et al.* has been discussed above. Dranoff *et al.* and Shao *et al.* do not even mention the WAP promoter or the use thereof for any purpose. Thus, the teachings in the Dranoff *et al.* and Shao *et al.* references are not relevant to Applicants' invention. Paleyanda *et al.* analyzed the "tissue-specific and developmental pattern of expression of a hybrid gene comprised of mWAP promoter fragment and the human protein C (HPC) gene" in transgenic mice. Paleyanda *et al.* do not teach

or even suggest that the WAP promoter can be used to express a heterologous gene in a human cell.

There are no teachings in the art cited which, in and of themselves, would direct the skilled person to obtain expression of a heterologous gene in human cells using the rodent WAP regulatory sequence or use a retroviral vector to do so. WAP is a rodent regulatory sequence and the cited art provides no suggestion or expectation of success that the rodent regulatory sequence can direct expression of a heterologous gene in human cells.

Dranoff *et al.* and Shao *et al.* do not even mention the MMTV promoter or the use thereof for any purpose. Thus, the teachings in the Dranoff *et al.* and Shao *et al.* references are not relevant to Applicants' invention. Paleyanda *et al.* analyzed the pattern of expression of a gene under the transcriptional control of the WAP promoter, but do not teach or even suggest that the WAP promoter can be used to express a heterologous gene in a human cell. Clearly, the combined teachings of the cited references, either alone or in combination, do not teach or even suggest expression of a heterologous gene in human cells using the rodent MMTV regulatory sequence.

As stated in the previously filed Amendment A, the obviousness rejection has been made with the advantage of impermissible hindsight, and is therefore, legally improper. That is, in making the obviousness rejection, the Examiner has read the prior art with the benefit of Applicant's disclosure in which there is a clear teaching that the rodent WAP regulatory sequences can direct expression of a heterologous gene in human cells and that the WAP regulatory sequences would do so using a retroviral vector. As the court made clear in *In re Dow*, it is not legally correct to rely on Applicant's disclosure for the suggestion that the cited references should be combined and the expectation of success. In the present case, the suggestion or motivation for combining the references and the expectation of success are not found in the prior art, but rather in Applicant's disclosure.

The combined teachings of Dranoff *et al.* in view of Paleyanda *et al.*, 1994, Shao *et al.* 1994 do not render obvious Applicants' claimed invention.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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